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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,068	11/14/2003	Meng Yang	312762002710	2630

25225 7590 12/09/2009

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
12/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,068	YANG ET AL.	
	Examiner	Art Unit	
	SAMUEL C. WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's reply filed 08/04/2009 is acknowledged. Claims 37 and 39 are pending.

The rejection of claim 39 under 35 USC 112, 1st paragraph made in the Office action mailed 05/05/2009 is withdrawn in view of Applicant's amendment.

The rejection of claims 37 and 39 under 35 USC 103(a) made in the Office action mailed 05/05/2009 is maintained and reiterated below. Applicant's arguments will be addressed following the rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Contag et al (US 5,650,135 prior art of record) in view of Okabe et al (FEBS Letters 407:313-319; 1997).

With regard to claim 37, Contag taught (column 25, line 25):

"Alternatively, an animal model for the study of putative anti-inflammatory substances can be made by making the animal transgenic for luciferase under the control of the E-selection promoter. Since E-selection is expressed at sites of inflammation, transgenic cells at sites of inflammation would express luciferase.

The system can be used to screen for anti-inflammatory substances. Inflammatory stimuli can be administered to control and experimental animals, and the effects of putative anti-inflammatory compounds evaluated by their effects on induced luminescence in treated animals relative to control animals."

This passage suggested *administering a test substance to said animal which expresses a* [light generating protein] *under the direction of a promoter of an endogenous gene, and determining the expression of said promoter via observing the presence, absence or intensity of the* [light] *generated by said* [light generating protein] *at various locations* [see above: "sites of inflammation"] *in said animal*, and further suggests *determining the expression of said endogenous promoter, via observing the presence, absence or intensity of the* [light] *generated by said* [light generating protein] *at various locations* [see above: "sites of inflammation"] *in a control laboratory animal which expresses said* [light generating protein] *under the direction of said promoter of said gene*, and further suggests *comparing the expression of said promoter determined*

in steps a) and b), wherein the expression determined in step a) is different from that in step b) when said test substance modulates said gene expression (implicitly taught by the phrase "evaluated by their effects on induced luminescence in treated animals relative to control animals").

In addition, while the cited passage taught luciferase, Contag also taught as alternatives yellow fluorescent protein (column 3, lines 2-5; column 9, lines 29-32) and green fluorescent protein (column 9, lines 29-32).

In addition, Contag also clearly taught "mammals" (see title, abstract, column 2, lines 58-62, for example). More specifically, Contag taught non-human mammals (i.e. mice; see for example figures 5 and 6).

In addition, Contag taught (column 3, lines 25-30):

"If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

With regard to the term "whole-body external fluorescent optical imaging", such term is explicitly defined in Applicant's specification (paragraph [0034] of the published application) as follows:

"As used herein, "whole-body external fluorescent optical imaging" refers to an imaging process in which the presence, absence or intensity of the fluorescence

generated by the fluorophore at various locations in the host organism is monitored, recorded and/or analyzed externally without any procedure, e.g., surgical procedure, to expose and/or to excise the desired observing site from the host organism."

This definition is so broad as to encompass merely "looking" at the animal. Furthermore, neither this definition, nor anything in the claim, requires the "various sites" to be internal to the animal. In this regard, Contag taught (column 15, line 62):

"In cases where it is possible to use light-generating moieties which are extremely bright, and/or to detect light-emitting conjugates localized near the surface of the subject or animal being imaged, a pair of "night-vision" goggles or a standard high-sensitivity video camera, such as a Silicon Intensified Tube (SIT) camera (e.g. Hamamatsu Photonic Systems, Bridgewater, N.J.), may be used. More typically, however, a more sensitive method of light detection is required."

Contag did not explicitly teach an embodiment where the method described at column 25, line 25 was performed wherein a) the animal was not restrained and b) green or yellow fluorescent protein was used in place of luciferase.

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in studying potential anti-inflammatory compounds, as suggested by Contag, where the sites of inflammation were at or near the surface (e.g. the skin), using yellow or green fluorescent protein instead of luciferase?

Okabe taught transgenic mice expressing the green fluorescent protein (see entire article). Of note, Okabe stated (page 313, section 2.3): "The expression of EGFP

in F1 pups from each transgenic founder mouse was examined by the naked eye or under a fluorescent microscope using excitation light." Also see caption, figure 1: "Although EGFP requires a blue excitation light (488 nm), emission of the green light was visible to the naked eye."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the EGFP taught by Okabe in place of the luciferase in the method described by Contag at column 25, line 25, for the purpose of studying potential anti-inflammatory compounds at sites of inflammation at or near the surface (e.g. the skin).

As Contag taught luciferase, yellow fluorescent protein and green fluorescent protein as equivalents for the purpose of his method, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one for the other, thus arriving at the limitations *fluorescent protein*, *fluorescence*, *fluorophore*, and *autofluorescent* recited in claim 37. Furthermore, one would have been motivated to avoid restraining the animal, thus allowing its movement, in order to avoid placing unnecessary stress on the animal. Finally, one would have been motivated to substitute the EGFP taught by Okabe in place of the luciferase, as Okabe expressly stated (sentence spanning pages 315-316): "The great advantage of the GFP as a reporter is that the introduction of a substrate is not required, unlike other commonly used reporter genes such as beta-galactosidase, firefly luciferase, alkaline phosphatase, chloramphenicol acetyltransferase and beta-glucuronidase. This enabled us to observe the fluorescence from live cells and in intact form on a real-time basis." Whether one were to merely

observe the mice with the naked eye, or use the "standard high-sensitivity video camera" suggested by Contag, either would qualify as "whole-body external fluorescent optical imaging".

Response to Arguments

Applicant's arguments filed 08/04/2009 have been fully considered but they are not persuasive. Applicant initially states:

> As to Contag, the Office asserts that the use of an E-selection promoter coupled to luciferase to evaluate drugs that affect inflammation is tantamount to screening for a modulator of the expression of a gene. Technically, this is correct; however, the claim is focused on gene regulation, not evaluating agents to treat particular reactions.

Applicant evidently agrees that Contag's method is, technically, screening for a modulator of the expression of a gene. Whereas the claim may be "focused" on gene regulation, and not on evaluating agents to treat particular reactions, Contag's method nevertheless evaluates the effect of drugs (modulators) on the expression of a gene (in this case, E-selectin). Therefore Contag's method meets this limitation.

Applicant continues:

> Contag does not suggest using techniques that involve mobile non-restrained animals despite the reference to an image that can be constructed in a short time scale relative to the time scale at which the un-immobilized subject moves. As taught by Contag at the bottom of column 15 at lines 55, *et seq.*, an important aspect of what they describe is a photodetector device with a high enough sensitivity to enable imaging of faint light from within a mammal in a reasonable amount of

time "preferably less than about 30 minutes." This time frame clearly cannot relate to a short time scale relative to the time scale at which the un-immobilized subject moves.

This is confirmed by the following text, extending through column 19 at line 40 which reveals that Contag is not even "observing" the presence, absence or intensity of fluorescence but rather counting photons in a complex manner.

With regard to the immobilization argument, it is clear that Contag contemplated situations in which the subject did not have to be immobilized:

Column 3, lines 25: "If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

Column 17, line 63: "If the signal is sufficiently bright that an image can be constructed from photon emission measured in less than about 20 milliseconds, and the subject is not particularly agitated, no special immobilization precautions may be required, except to insure that the subject is in the field of the detection device at the start of the measuring period.

Applicant may take the position that Contag's remark "preferably less than about 30 minutes" indicated that Contag's technology was limited to 30 minutes (i.e. that his method required 30 minutes to collect the photons for the image). The examiner does not see this to be the case, given Contag's remark "less than about 20 millisecond" at column 17, line 63.

Furthermore, when considering the prior art as a whole (i.e. Contag *in view of* Okabe), one of skill would have clearly understood that animals need not be immobilized in certain situations, since Okabe taught that when observing transgenic mice expressing GFP, fluorescence was visible to the naked eye. If the signal (in Okabe's case, from GFP) were visible to the naked eye, then it would also be strong enough to be detected by an imaging device without having to immobilize the subject.

Applicant also argues extensively that Contag "teaches away" from using fluorescent proteins such as GFP. The examiner respectfully disagrees with this assertion. While Contag may point out particular advantages for bioluminescent markers (e.g. luciferase), this does not constitute a teachings away from fluorescent proteins, which Contag clearly contemplates as useful for his invention (column 7, lines 13-39, emphasis provided): "The present invention includes methods and compositions relating to non-invasive imaging and/or detecting of light-emitting conjugates in mammalian subjects. The conjugates contain a biocompatible entity and a light-generating moiety...For example, in the case where the entities are the cells constituting the mammalian subject being imaged, the light-generating moiety may be a bioluminescent or fluorescent protein "conjugated" to the cells through localized, promoter-controlled expression…". See also MPEP 2123(II): "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971)."

Applicant further argues:

But the combination of Okabe with Contag actually teaches away from the invention. Okabe teaches production of green fluorescent protein under control of a chicken β actin promoter and a cytomegalovirus enhancer resulting in all of the tissues, with the exception of erythrocytes and hair, being green in response to ultraviolet light. Combining Okabe with Contag, then, would not permit the localization of gene expression as required by the claims, since the GFP is ubiquitously expressed. Therefore, this combination does not result in or suggest the claimed invention.

This argument is not persuasive. The rejection did not assert that one would have been motivated to evaluate changes in gene expression using the chicken β actin promoter. The rejection stated: "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the EGFP taught by Okabe in place of the luciferase in the method described by Contag at column 25, line 25, for the purpose of studying potential anti-inflammatory compounds at sites of inflammation at or near the surface (e.g. the skin)." One of ordinary skill in the art had enough intelligence to realize that if the goal were to determine how various drugs affected expression from the E-selectin promoter (which is what Contag was concerned with), then one had better place GFP expression under the E-selectin promoter, not chicken β actin promoter. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference (i.e. using chicken β actin promoter-driven GFP in a method for evaluating E-selectin expression). Rather, the test is what the combined teachings of the references

would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin (US 6,380,458 prior art of record) in view of Contag et al (US 5,650,135 prior art of record) and Okabe et al (FEBS Letters 407:313-319; 1997).

Lin taught the creation of genetically modified zebrafish expressing green fluorescent protein (column 7, line 11: "A preferred reporter protein that can be directly detected is the green fluorescent protein (GFP).").

Lin also taught (column 11, lines 10-18):

"The disclosed transgenic fish can be used in combination with these and other mutations to assess the effect of a mutant gene on the expression of a gene of interest. For example, mutations can be introduced into strains of transgenic fish harboring an exogenous construct containing the expression sequences of a fish gene of interest operably linked to a sequence encoding a reporter protein. By comparing the expression of the reporter protein in fish with a mutation to those without the mutation, the effect of the mutation on the expression of the gene from which the expression sequences are derived can be assessed." By "mutations can be introduced into strains of transgenic fish", one of skill in the art would have understood that, in order to introduce the mutation to a strain of fish, the mutation would have to be introduced into the germ line (otherwise there would be one fish, not a strain, with the mutation in one

cell, which would not have been realistically suitable for "comparing the expression of the reporter protein in fish with a mutation to those without the mutation").

Lin did not teach that the animals were non-human mammals, or that they were not restrained during observation.

Contag taught imaging light generating compounds including yellow and green fluorescent proteins (see abstract; column 9, lines 29-32).

In addition, Contag also clearly taught "mammals" (see title, abstract, column 2, lines 58-62, for example). More specifically, Contag taught non-human mammals (i.e. mice; see for example figures 5 and 6).

In addition, Contag taught (column 3, lines 25-30):

"If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

With regard to the term "whole-body external fluorescent optical imaging", such term is explicitly defined in Applicant's specification (paragraph [0034] of the published application) as follows:

"As used herein, "whole-body external fluorescent optical imaging" refers to an imaging process in which the presence, absence or intensity of the fluorescence generated by the fluorophore at various locations in the host organism is monitored,

recorded and/or analyzed externally without any procedure, e.g., surgical procedure, to expose and/or to excise the desired observing site from the host organism."

This definition is so broad as to encompass merely "looking" at the animal. Furthermore, neither this definition, nor nothing in the claim, requires the "various sites" to be internal to the animal. In this regard, Contag taught (column 15, line 62):

"In cases where it is possible to use light-generating moieties which are extremely bright, and/or to detect light-emitting conjugates localized near the surface of the subject or animal being imaged, a pair of "night-vision" goggles or a standard high-sensitivity video camera, such as a Silicon Intensified Tube (SIT) camera (e.g. Hamamatsu Photonic Systems, Bridgewater, N.J.), may be used. More typically, however, a more sensitive method of light detection is required."

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in substituting mice expressing GFP in place of the fish expressing GFP in the method taught by Lin?

Okabe taught transgenic mice expressing the green fluorescent protein (see entire article). Of note, Okabe stated (page 313, section 2.3): "The expression of EGFP in F1 pups from each transgenic founder mouse was examined by the naked eye or under a fluorescent microscope using excitation light." Also see caption, figure 1: "Although EGFP requires a blue excitation light (488 nm), emission of the green light was visible to the naked eye."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the EGFP expressing mice taught by Okabe

(and, correspondingly, an endogenous mouse promoter in place of a fish promoter) in place of the GFP expressing fish in the method described by Lin at column 11, lines 10-18, since one of ordinary skill in the art would have clearly recognized the equivalent use of mice in place of fish, and based on the disclosures of Okabe and Contag, one would have had a reasonable expectation of success in observing the effects of a genetically engineered mutation on a gene of interest in cases where the sites being observed were at or near the surface of the animal.

Furthermore, one would have been motivated to avoid restraining the animal, thus allowing its movement, in order to avoid placing unnecessary stress on the animal. Whether one were to merely observe the mice with the naked eye, or use the "standard high-sensitivity video camera" suggested by Contag, either would qualify as "whole-body external fluorescent optical imaging".

Response to Arguments

Applicant's arguments filed 08/04/2009 have been fully considered but they are not persuasive. Applicant argues:

> That method is fine for zebra fish, which are transparent. It leaves the problem of real-time whole body fluorescence observations in animals that are not transparent, specifically mammals, to be solved by the present inventors.

> This solution is not provided by combining Lin with Contag and Okabe for the same reasons set forth above. As noted, Contag teaches away from using fluorescent protein as a label for imaging mammals and Okabe specifically prevents noting the locations of the expression of the gene as required by the claims.

As a preliminary matter, it is noted that the rejections of both claims 37 and 39 is based in part on the obviousness of visualizing GFP expression at or near the surface of the animal (e.g. the skin), which Okabe showed was clearly possible. Therefore, to observe GFP expression in living, mobile, unrestrained mammals, the mammals need not be transparent. The claims do not recite "in the spleen" or "in the kidneys", for example.

In addition, the argument that Okabe teaches away from fluorescent proteins has already been addressed.

Finally, the argument that "Okabe specifically prevents noting the locations of the expression of the gene as required by the claims" is evidently directed to the fact that Okabe used a promoter that resulted in ubiquitous expression of the GFP in all tissues. It is noted that the primary reference, Lin, discussed observing the effects of mutations on expression of a "gene of interest" by making a "construct containing the expression sequences of fish gene of interest operably linked to a sequence encoding a reporter gene". Therefore, unless the "gene of interest" was ubiquitously expressed, one would in fact be observing the expression in those locations where the "gene of interest" was expressed. Furthermore, even if the "gene of interest" was ubiquitously expressed (i.e. in all tissues), this is not inconsistent with the claims. The claims do not require that fluorescence only occurs in particular locations. The claims only require "observing the presence, absence or intensity of the fluorescence generated by said fluorophore at various locations". Even if the whole animal were green, one would fulfill the limitation by observing the ears, eyes, tail, etc.

For the reasons discussed above, the rejections are still considered proper and are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637

/Young J Kim/
Primary Examiner, Art Unit 1637